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Benzodiazepines: Uses and Abuses

SUMMARY

Anxiety is ubiquitous in our society. Although non-drug treatments should always be used, benzodiazepines are the drugs of choice when drugs are indicated. In double blind studies the benzodiazepines are superior to placebo in controlling acute anxiety and autonomic over-activity in psychosomatic disorders. They are also useful in a variety of other conditions such as the treatment or prevention of muscle spasms and pain, status epilepticus, drug withdrawal, stage 4 sleep disorders and akathisia. However, benzodiazepines have many side effects, produce tolerance, dependence and withdrawal syndromes and should be used cautiously. There is no evidence that benzodiazepines are useful in chronic anxiety. The short-acting drugs are safer with elderly patients and those with hepatic disease or hypoalbuminemia. Small amounts of prescription benzodiazepines should be used for the shortest possible period. Educational programs concerning the proper use of benzodiazepines should be increased. (Can Fam Physician 1982; 28:1630-1639).

SOMMAIRE

L'anxiété est omniprésente dans notre société. Bien qu'on devrait toujours faire usage de thérapies non-médicamenteuses, les benzodiazépines sont des médicaments de choix lorsqu'une médication est indiquée. Dans des études à double insu, les benzodiazépines sont supérieures aux placebo pour contrôler l'anxiété aiguë et la suractivité dans les troubles psychosomatiques. Elles sont aussi utiles pour une variété d'autres états tels que le traitement ou la prévention des spasmes et douleurs musculaires, le status epilepticus, le syndrome de sevrage médicamenteux, les troubles du sommeil de stade 4 et l'akathisie. Toutefois, les benzodiazépines comportent de nombreux effets secondaires, occasionnent les syndromes de tolérance, de dépendance et de retrait et on devrait en faire un usage prudent. Il n'y a pas d'évidence que les benzodiazépines soient utiles dans le traitement de l'anxiété chronique. Les médicaments à courte durée d'action sont plus sûrs pour les personnes âgées et celles souffrant de maladie hépatique ou d'hypoalbuminémie. Des prescriptions de petites quantités de benzodiazépines devraient être faites pour une période la plus courte possible. On devrait augmenter le nombre de programmes éducationnels concernant l'usage approprié des benzodiazépines.

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THE EFFICACY and ethics of using minor tranquilizers are frequently debated in our society. Two opposite points of view emerge. The 'conservative-stoic' view is that anxiety is normal and must be coped with; the person who resorts to using benzodiazepines is weak in character and the use of such pills will decrease his willpower, motivation and problem-solving abilities.^{1, 2} This viewpoint blames the overuse of these drugs on the physician for over-prescribing, the

patient for being too demanding and the pharmaceutical industry for excessive advertising.^{3, 4}

In the 'liberal' view, a person in this highly complex, technological, anxiety-provoking society has the right to use any available methods to cope with his individual stresses.³ The benzodiazepines are the least of several evils—they are less dangerous than incapacitating anxiety, alcoholism or other addictions.

These two extreme views ignore a

rational approach based on knowing who takes benzodiazepines and why, for what conditions, with what efficacy and with what dangers. It is important to know how these drugs work, what alternative coping mechanisms and treatments are available and how the decision to use medication is reached.

Extent of Use

Over 10% of adult Canadians and Americans take benzodiazepines by prescription in any one year.⁵ This is similar to rates in Europe, although France and Belgium have even higher rates.³ The use of minor tranquilizers is more common than the total use of all other psychotropic medications, including antidepressants and antipsychotics. Diazepam is probably the most commonly used drug in the western world.

Females take these drugs twice as frequently as males (20% versus 8%).^{3, 6} We do not know whether this is due to role stereotyping, the nature of the relationship between female patients and male physicians, or the biological concomitants of being female (menstrual cycle, pregnancy, childbirth, and menopause). Probably males more frequently employ other remedies for anxiety, including the use of alcohol and marijuana.

Similarly, the elderly receive a disproportionate number of prescriptions for benzodiazepines.^{5, 7} They are more likely to have difficulty metabolizing the long-acting benzodiazepines and are therefore more likely to have unwanted side effects and toxicity.^{2, 8, 9} They are also more likely to be taking other drugs and to suffer from complex drug regimens and interactions. Although the depressive syndromes are more prevalent in this age group, antidepressants are as underused as tranquilizers are overused.⁴

Most prescriptions for benzodiazepines are written by family physicians and internists.^{3, 6} Of patients who have used a psychotherapeutic drug, 85% have never seen a psychiatrist. A national survey³ showed that benzodiazepines were prescribed for the following diagnoses:

1. Mental disorder (anxiety, depression etc.) (37%)
2. Senility and related symptoms (17%)
3. Physical disorders (circulatory,

respiratory, digestive, skin, etc.) (46%)

Patients with physical disorders are given benzodiazepines as frequently, even though the basic indications for prescribing these drugs are the prevention or alleviation of psychic and emotional distress.^{6, 10}

The stereotyped image of the benzodiazepine abuser is a pill-popping, bored, middle-class, self-indulgent, young suburban housewife. In fact, benzodiazepine abusers are most frequently middle-aged housewives (working outside the home or not) from the lowest socioeconomic stratum with less than grade school education, trying to cope with many real biological, psychological and socio-cultural problems.³

Pharmacological Action

All the benzodiazepines are similar in structure and pharmacological action. Although differences in their metabolism include absorption, distribution, degradation and excretion, these must be interpreted cautiously because of high variation in individuals' metabolism and sensitivity to the clinical effects of benzodiazepines. For instance, the dose of diazepam required for relaxation for gastroscopy may vary 22-fold.² Nevertheless, rational use of the benzodiazepines does require some knowledge of the various compounds' pharmacokinetics.

The benzodiazepines can be divided into two groups based on the half-lives of parent compounds and their active metabolites: the long-acting and the short-acting groups.^{2, 5, 8, 11-13} (See Table 1.)

TABLE 1
Half Lives (Hours) of
Benzodiazepines Marketed in Canada

Long-Acting Drugs		Short-Acting Drugs	
Clorazepate	50-100	Oxazepam	5-20
Flurazepam	40-100	Lorazepam	10-15
Diazepam	20-50	Triazolam	2- 5
Chlordiazepoxide			
	5-30	Temazepam	8-10
Nitrazolam	18-28	Bromazepam	10-15
Ketazolam	30-50	Alprazolam	6-20
Clonazepam	18-50		

The long-acting drugs accumulate when taken daily. They are converted in the liver to active metabolites, which also have long half-lives. There may be excessive sedation the next morning or several days later, even on a fixed dose. Oral administration of

chlordiazepoxide or diazepam produces more rapid and reliable clinical effects than IM injections of the same dose. IM administration results in delayed and incomplete absorption of chlordiazepoxide and diazepam, as well as delayed appearance of their active desmethyl metabolites, because the drug crystallizes in muscles. Elderly patients and those with hepatic disease metabolize these drugs more slowly and are more likely to have side effects or toxicity. They should therefore receive only half of the usual dose. Some of the long-acting benzodiazepines (e.g., diazepam) are quickly absorbed and highly lipid soluble so that they have a rapid onset of action. They may be useful hypnotics in the short term.

Conversion of the short-acting drugs by conjugation to an inactive glucuronide is extrahepatic and is not decreased by age or liver disease.^{2, 8, 12, 13} Therefore, cumulative effects during prolonged therapy are much less significant than with the long-acting drugs. If the short-acting drugs are used as daytime anxiolytics, divided doses (at least bid) are required. Maximum effects are reached within a few days and residual effects terminate quickly.

Neurotransmitters

The effects of the benzodiazepines are mediated by several distinct mechanisms.¹⁴⁻¹⁶ The neurotransmitters that have been implicated include norepinephrine, serotonin, GABA and glycine. Specific benzodiazepine receptors have been identified in human brain tissue,¹⁷ suggesting that there may be specific benzodiazepine-like molecules in the brain whose activity produces an endogenous anxiolytic effect.

Stimulation of the benzodiazepine receptors enhances the effects of GABA, the principal inhibiting neurotransmitter.^{8, 14} The resulting depolarization and decreased production of norepinephrine and serotonin cause sedation and anti-anxiety effects by decreasing electrical activity in the punishment and inhibitory areas of the brain. Diazepam is also a glycine receptor stimulator; because glycine normally inhibits motor neurones, diazepam functions as a muscle relaxant.

Uses of Benzodiazepines

In animals, these drugs cause disin-

hibition, and an increase in spontaneous and exploratory activity.⁸ They suppress operant avoidance behavior and restore behavior suppressed by punishment.^{15, 18} They attenuate the effects of stress and frustration, and decrease aggression and hostility. In humans, the benzodiazepines appear to influence these same behaviors, reducing acute anxiety and accompanying inhibition.

In Anxiety

The benzodiazepines have a wide variety of uses⁸ (see Table 2). They are more effective than barbiturates and meprobamate in controlling anxiety with less sedation and other central nervous system side effects. They are less prone to abuse and addiction, less dangerous in overdose, and cause less microsomal enzyme induction in the liver, so that there are fewer drug interactions.

TABLE 2
Uses of Benzodiazepines

1. Neurotic anxiety
2. Agitated depression
3. Side effects from antidepressants and neuroleptics
4. Hallucinogenic psychosis
5. Neuromuscular diseases
6. Seizures
—status epilepticus
—other
7. Alcohol withdrawal
8. Sleep disturbances
—stage 4 disorders
—? insomnia
9. Anesthesia and surgery
10. Psychosomatic disorders (with primary/secondary anxiety)

Anxiety attacks have a short duration and therefore patients will frequently have a spontaneous remission.⁴ In addition, anxious patients will respond to a placebo 50% of the time.⁴ Because of this, a practitioner who prescribes anxiolytics after an initial assessment may be misled by the positive response that many patients report. Nevertheless, these drugs have proven more effective than placebo in double blind trials with non-psychotic anxious patients.^{8, 11}

In recurrent panic disorders, the tricyclic antidepressants are generally more useful. Acute anxiety attacks tend to be self-limiting and if the severity is mild or moderate, non-pharmacological treatments should be

tried. These treatments include reassurance, ventilation, exploration of the symbolic meanings of stressors, problem solving, relaxation training, socialization, and desensitization.¹⁹ If acute anxiety is severe or if chronic anxiety presents with marked flare-ups, then benzodiazepines may be useful for a short and strictly-enforced period of time (two to four weeks). PRN use to a daily limit may be preferable to a fixed dosage schedule when symptom severity varies.

In Depression

The depressive syndrome includes a dysphoric mood, loss of appetite and weight, loss of sleep with early morning awakening, and a diurnal variation in which a patient feels worse in the morning and better as the day progresses. The treatment of choice is an adequate trial of antidepressants, although minor tranquilizers may be useful if agitation is also present. The benzodiazepines are not useful in schizophrenic decompensations, although they are useful in the acute psychoses caused by hallucinogens. Sometimes the antidepressants cause restlessness or agitation as a side effect during the treatment of depression and, somewhat more frequently, the neuroleptics cause akathisia, which is an extrapyramidal side effect. The benzodiazepines may be useful for these symptoms.²⁰

In Neuromuscular Conditions

The benzodiazepines facilitate the action of brain stem inhibitory interneurons, with less effect on the spinal cord, and this causes muscle relaxation which may be beneficial in neuromuscular conditions (see Table 3).

TABLE 3
Musculoskeletal Disorders That Benefit from Benzodiazepines

Cerebral palsy
Multiple sclerosis
Parkinsonism
Amyotrophic lateral sclerosis
Cerebral vascular accidents
Traumatic spinal cord lesions
Disc disease
Muscle strains and sprains

In Seizure Disorders

While diazepam is extremely useful in status epilepticus, it is less useful in seizure prophylaxis. Diazepam inhibits the propagation and generalization

of seizure activity originating from a focus. It has a similar molecular configuration to diphenylhydantoin and may interact with similar receptor sites in the CNS.⁸ Nitrazepam appears to have more antiepileptic activity and has been used prophylactically with grand-mal seizures and infantile spasms. Clonazepam²¹ is used in the treatment of absence seizures refractory to ethosuximide or valproic acid, and in seizure disorders associated with myoclonus.

In Alcohol Withdrawal

Benzodiazepines are also widely used to attenuate alcohol withdrawal states, especially delirium tremens. Although they do decrease severe withdrawal complications they do not alter the subsequent drinking pattern. Alcoholics often tend to abuse these drugs and run the risk of a double addiction.

In Sleep Disorders

Benzodiazepines do decrease Stage 4 sleep and are useful in treating somnambulism, enuresis and night terrors, which are Stage 4 disorders. Their use in simple insomnia is more controversial, because tolerance to their hypnotic effect occurs quickly (less than one week).⁸

The benzodiazepines decrease REM sleep or dreaming less than other hypnotics such as barbiturates, glutethimide, methylprylon and possibly chloral hydrate.⁸ The subjective unpleasantness of REM sleep and dream rebound does not occur when benzodiazepines are withdrawn, although rebound insomnia is reported. The danger of hypnotic drug dependence is less than with barbiturates.

As hypnotics, the short-acting benzodiazepines are superior to the long-acting drugs because they do not accumulate as much, thereby lessening daytime sedation, cognitive and motor impairment or toxicity. However, the short-acting benzodiazepines may increase the incidence of rebound insomnia and withdrawal symptoms. Although benzodiazepines are effective in acute situational insomnia (e.g., jet lag, grief reaction or hospitalization), they should not be routinely used, especially where reassurance, support, relaxation, and exploration of personal difficulties are likely to be effective. Severe insomnia may require investigation at a sleep laboratory.

In Anesthesia and Analgesia

The benzodiazepines have a number of applications in anesthesia, labor and surgery.⁸ They are used in endoscopy and before general anesthesia or cardioversion. They increase analgesia, decrease opiate requirements and enhance subjective amnesia. The usual clinical doses given before delivery cause no important adverse effects upon the neonate. However, in high doses they have been associated with prolonged neonatal lethargy, hypotonia, hypothermia and respiratory depression. In anesthesia, surgery and labor, the short-acting drugs should be used more commonly.

In Psychosomatic Disorders

The benzodiazepines are frequently used in organic or psychosomatic disorders in which anxiety is believed to have a precipitating or exacerbating role.¹³ Lasagna⁶ and Ayd²² reviewed the literature on the effects of benzodiazepines on psychosomatic illnesses. They reported that lorazepam decreased anxiety, hypertension and gastrointestinal complaints, including aerophagy, irritable colon and nervous dyspepsia. Diazepam resulted in decreased gastric secretion when patients with duodenal ulcer and dyspepsia were stimulated by pentagastrin.⁶ Chlordiazepoxide resulted in less narcotic use in the first 24 hours on a coronary care unit than amobarbital. In the treatment of essential hypertension, Lasagna speculates that benzodiazepines may be more useful than phenobarbital and antihypertensive drugs, which result in significant side effects and non-compliance. In coronary artery disease, benzodiazepines may be useful in allaying anxiety and autonomic overactivity. They may decrease the incidence of arrhythmias and sudden death in coronary care units.

Unwanted Effects And Hazards

Neurological effects^{2, 8, 23} include depression, fatigue, drowsiness, somnolence, muscle weakness, nystagmus, and dysarthria. These effects are dose-dependent and are more likely to occur in the elderly, and in those with low serum albumen. Sedation occurs in 3% of patients (9% if the serum albumen is low, since benzodiazepines are normally bound to

serum albumen). Residual daytime sedation and mild cognitive impairment are more likely to occur with the long-acting drugs.

Psychological effects occasionally occur and include sleep disturbances such as rebound insomnia²⁴ hypnagogic hallucinations and nightmares. Acute depression and suicidal ideation are reported. Paradoxical rage reactions may occur, particularly in those whose anger is kept in check by their anxiety, who are frustrated by their environment or who have a history of outbursts and impulsiveness.^{8, 9}

With intravenous diazepam, occasional pain or phlebitis will occur at the injection site. Life-threatening adverse reactions, including respiratory depression and cardiac arrest, occur in 1.7% of patients after IV diazepam, especially if severe pulmonary or cardiovascular disease exists. IV diazepam should be given slowly (less than 2.5 mg/min.)⁹ and only in settings where cardiopulmonary support systems are available.

Drug abuse and addiction have been reported. Any benzodiazepine can be abused and produce physiological addiction if large doses are taken over a long period of time. This danger is much less than with other drugs.⁸ Although addiction is rare, withdrawal effects have been reported including anxiety, tremor, insomnia, nausea and vomiting. These symptoms occur three to ten days after withdrawal of long-acting benzodiazepines and within 24 hours of withdrawing short-acting drugs.²⁴ They are rare when short courses are given at recommended therapeutic dosage. These symptoms, whether psychological or physiological in origin, may falsely convince the patient or doctor of the need for continuing medication. Those patients motivated to discontinue the drug should be encouraged.

Successful withdrawal can be accomplished by dividing the total daily dose into four spaced administrations. This interrupts the usual pattern of drug-taking immediately before anticipated stresses. Successive reductions of 2-5 mg (in diazepam equivalents) each can be made at the administration time chosen by the patient. Each reduction may be followed by several days of mild anxiety and physiological arousal. When this settles, the patient is ready for the next reduction. Explanation of the pharmacology and physi-

Keflex[®] cephalixin

DESCRIPTION: Keflex is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7 (D amino acid phenylacetamido) 3 methyl 3 cephem 4 carboxylic acid monohydrate.

ACTION: Cephalixin is bactericidal against many gram positive and gram negative organisms. In vitro tests demonstrate that the cephalosporins are bactericidal through their inhibition of cell wall synthesis.

INDICATIONS: Keflex may be indicated in the treatment of bacterial infections of the respiratory tract, including otitis media, genitourinary tract, bones and joints, skin and soft tissue when the infection is caused by susceptible organisms.

CONTRAINDICATIONS: Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

PRECAUTIONS: Antibiotics, including Keflex, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

In penicillin allergic patients, cephalosporin antibiotics should be used with caution. There is some evidence of partial cross allergenicity of the penicillins and the cephalosporins. Of 7450 clinical trial patients, 291 had histories of penicillin allergy. Nineteen of them (about 6.5 percent) were among those in whom possible allergic reactions to cephalixin were observed.

Patients should be followed carefully so that any side effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflex occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keflex may result in overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Keflex should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

If Keflex is to be used for long term therapy, periodic monitoring of hematology, renal and hepatic functions should be done. Indicated surgical procedures should be performed in conjunction with antibiotic therapy, e.g., the incision and drainage of abscesses.

Safety of this product for use during pregnancy has not been established.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

In patients being treated with Keflex, a false positive reaction for glucose in the urine may occur with Benedict's or Fehling's solutions or with Clintest tablets, but not with Tes Tape.

ADVERSE REACTIONS: Gastro-intestinal—Diarrhea has been reported in only 1.5 percent of 7450 clinical trial patients. It was very rarely severe enough to warrant cessation of therapy. Nausea, vomiting, dyspepsia and abdominal pain have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, leucopenia due to neutropenia, and slight elevations in SGOT and SGPT have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSE: No information is available on the treatment of overdose with Keflex. There is no specific antidote.

MICROBIOLOGY: Keflex is active against the following organisms in vitro.

Beta hemolytic and other streptococci (many strains of enterococci, e.g., *Streptococcus faecalis*, are resistant).

Staphylococci, including coagulase positive, coagulase negative, and penicillinase producing strains (a few strains of staphylococci are resistant to cephalixin).

Diplococcus pneumoniae	Hemophilus influenzae
Escherichia coli	Proteus mirabilis
Klebsiella pneumoniae	Neisseria catarrhalis

Keflex is not active against most strains of *Enterobacter* sp., *Pr. morgani*, and *Pr. vulgaris*. It has no activity against *Pseudomonas* or *Herellea* species. When tested by in vitro methods, staphylococci exhibit cross resistance between Keflex and methicillin type antibiotics.

DOSEAGE AND ADMINISTRATION: Keflex is administered orally. The adult dosage ranges from 1 to 4 g daily in divided doses. The usual adult dose is 250 mg every six hours. For more severe infections or those caused by less susceptible organisms, larger doses may be needed. If daily doses of Keflex greater than 4 g are required, parenteral cephalosporins, in appropriate doses should be considered. The recommended daily dosage for children is 25 to 50 mg per kg divided into four doses.

Keflex Suspension

Child's Weight	125 mg/5 ml	250 mg/5 ml
10 kg (22 lb)	1 to 1 tsp q.i.d.	
20 kg (44 lb)	1 to 2 tsp q.i.d.	1 to 1 tsp q.i.d.
40 kg (88 lb)	2 to 4 tsp q.i.d.	1 to 2 tsp q.i.d.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage of 75 to 100 mg per kg per day in four divided doses is required.

In the treatment of beta hemolytic streptococcal infections, antibiotic therapy should be administered for at least ten days.

To obtain maximum peak levels, cephalixin should be administered on an empty stomach.

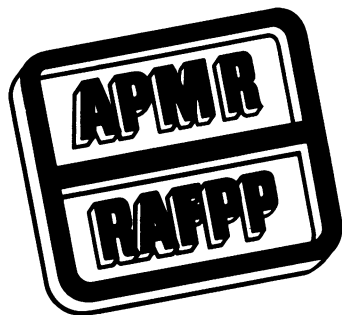
DOSEAGE FORMS:

Tablets Keflex, equivalent to 250 mg cephalixin (No. 1894). Identical Code U57 are supplied in bottles of 100 and 500.

Tablets Keflex, equivalent to 500 mg cephalixin (No. 1895). Identical Code U49 are supplied in bottles of 100 and 500.

Keflex for Oral Suspension, equivalent to 125 mg cephalixin per 5 ml teaspoonful, is supplied in a 100 ml size package (No. M201). Identical Code W21.

Keflex for Oral Suspension, equivalent to 250 mg cephalixin per 5 ml teaspoonful, is supplied in a 100 ml size package (No. M202). Identical Code W68.



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ology of drug withdrawal is extremely useful and supportive.

Of overdosed patients presenting at an emergency department, 31% have taken benzodiazepines.² These are rarely fatal unless combined with other drugs. The benzodiazepines potentiate the sedative and lethal effects of alcohol and other CNS depressants, and this combination, if abused, may interfere with cognitive, intellectual and psychomotor functioning. Dependence on benzodiazepines is more likely to occur with alcoholics, even if their drinking pattern doesn't change.

On the other hand, caffeine or caffeine-containing beverages may counteract the effects of the benzodiazepines,²⁶ so that the patient continues taking a minor tranquilizer or increases the dose unnecessarily.

Benzodiazepines are not well absorbed in the presence of antacids, achlorhydria, or anticholinergic drugs. Diazepam is a highly lipid soluble agent and should not be given with mineral oil, which will prevent its absorption.

Benzodiazepines are not entirely safe during pregnancy or the postnatal period. They have been associated, if used in the first trimester, with cleft lips and palates.²⁵ High doses at delivery may produce the 'floppy infant' syndrome, characterized by apnea, hypotonia, poor sucking, risk of aspiration and hypothermia.²² Diazepam and other benzodiazepines readily cross the placenta and reach higher concentrations in the fetal circulation than in maternal blood. They are also excreted in breast milk.²²

Conclusions

Benzodiazepines are more effective and safer than barbiturates, meprobamate or alcohol. In double-blind trials they have been shown to be superior to placebo in treating acute anxiety, in controlling anxiety and sympathetic over-activity in psychosomatic disorders and in treating muscle spasms from many causes.^{4, 8, 11}

However, the routine treatment of anxiety should involve other approaches before the prescription of benzodiazepines. In acute anxiety of mild or moderate severity, supportive psychotherapy, environmental manipulation or relaxation training may be preferred treatment.¹⁹ In severe acute anxiety, benzodiazepines may be use-

ful for a short period of time—less than four weeks. In chronic anxiety of moderate or severe intensity, benzodiazepines show no superiority over placebo. Continuous use should be avoided; medication should be reserved for prn use in acute or intolerable flare-ups. Often the mere availability of medication is sufficient reassurance to make this use unnecessary. Consultation with a psychiatrist or therapist should be considered, particularly before committing any patient to continuous longterm drug use.

Benzodiazepines should be used cautiously in all age groups and should be used less frequently with increasing age. Short-acting benzodiazepines are preferable to long-acting ones in all age groups, especially the elderly. Patients over 65 should be given half the usual daily dose.^{2, 5, 13} Long-acting cumulative drugs should be reserved for conditions where daytime sedation is acceptable, e.g., acute alcohol withdrawal or brief applications requiring a combination of night-time hypnotic and daytime anxiolytic given in a single bedtime dose.

Longterm use of these drugs (for more than one month) is of minimal or no pharmacological benefit and should be discouraged. A small percentage of users (10-13%) refuse to stop, decrease or change their use of benzodiazepines. Most of these patients have been using the drug for years. Having them stop these drugs may do them more harm than good.⁵

Continuing medical education programs on the use of minor tranquilizers could also be improved. Education of family physicians in a university-based hospital using audiovisual programs and feedback has been shown to improve prescription patterns; in a controlled study it was shown to be more effective than giving simple guidelines.⁵ Each physician who practices within a hospital could receive a computer-generated profile of his or her prescribing pattern compared with the patterns of other physicians. Audits or rounds should be conducted to discuss the reasons for individual variations of prescribing practices.

In teaching hospitals, staff physicians should countersign orders for problem drugs and promote discussion about benzodiazepine prescribing.

Some educational feedback programs have not decreased the number of prescriptions, but changed the pre-

Tagamet® (cimetidine)

PHARMACOLOGICAL CLASSIFICATION

Histamine H₂-Receptor Antagonist

ACTION

Cimetidine competitively inhibits the action of histamine at the histamine H₂-receptor. It inhibits daytime and nocturnal basal gastric acid secretion and also gastric acid secretion stimulated by food, histamine, pentagastrin, caffeine and insulin. Total pepsin output is reduced as a result of the decrease in volume of gastric juice. Cimetidine has no effect on the rate of gastric emptying or lower esophageal sphincter pressure.

INDICATIONS

- Duodenal ulcer and prophylaxis of recurrent duodenal ulcer
- Non-malignant gastric ulcer
- Gastroesophageal reflux disease
- Management of upper gastrointestinal hemorrhage
- Pathological hypersecretion associated with Zollinger-Ellison Syndrome, systemic mastocytosis and multiple endocrine adenomas.
- Prophylaxis of stress ulceration
- Prophylaxis of acid aspiration pneumonitis

CONTRAINDICATIONS

None known.

PRECAUTIONS

Use in Pregnancy, Nursing Mothers: Experience in pregnant patients is limited. Animal studies have revealed no evidence of impaired fertility or harm to the fetus. 'Tagamet' crosses the placental barrier. It is secreted in human milk. Anticipated benefits should be weighed against potential risks. 'Tagamet' has been used in clinical trials for the prevention of acid aspiration pneumonitis in women undergoing cesarean section or vaginal delivery without harm to the fetus.

Use in Children: In limited experience, 20-40 mg/kg/day has been administered in divided doses by mouth or intravenously. Anticipated benefits should be weighed against potential risks.

Use in Impaired Renal Function: A reduced dosage should be administered to patients with impaired renal function. (See DOSAGE AND ADMINISTRATION.)

Drug Interactions: 'Tagamet' may reduce the hepatic metabolism of warfarin-type anticoagulants, phenytoin, propranolol, chlorzazepoxide, diazepam and theophylline, thereby causing increased blood levels of these drugs. Benzodiazepines metabolized by other systems do not exhibit this effect. Since clinically significant effects have been reported with warfarin anticoagulants, close monitoring of prothrombin time is recommended, and adjustment of anticoagulant dose may be necessary.

Use in Gastric Ulcer: Symptomatic response to 'Tagamet' does not preclude the presence of a gastric malignancy.

Rapid Intravenous Injection: Rare cases of cardiac arrhythmias and hypotension have been reported following the rapid administration of 'Tagamet' Injection by intravenous bolus. (See DOSAGE AND ADMINISTRATION.)

ADVERSE REACTIONS

Mild and transient diarrhea, tiredness, dizziness and rash have occurred in a small number of patients. A few patients have developed mild, reversible gynecomastia during prolonged treatment. A few cases of the following have been reported: decreased white blood cell counts (including agranulocytosis), thrombocytopenia, aplastic anemia; reversible confusional states, usually in elderly and/or severely ill patients with renal insufficiency or organic brain syndrome; fever; hepatitis; interstitial nephritis; pancreatitis; small increases in plasma creatinine and serum transaminases.

OVERDOSAGE

Oral ingestion of up to 20 grams has caused no untoward effects. Recovery has been uneventful.

Treatment: Emesis and/or gastric lavage, monitoring and supportive therapy. Assisted respiration may be of value.

DOSAGE AND ADMINISTRATION - ADULTS (Experience in children is limited - see PRECAUTIONS.)

In clinical studies, 'Tagamet' has been used in divided doses of up to 2400 mg per day.

ACTIVE DUODENAL ULCER, NON-MALIGNANT GASTRIC ULCER, GASTROESOPHAGEAL REFLUX DISEASE

600 mg twice a day (at breakfast and bedtime) or 300 mg four times a day (with meals and at bedtime). Therapy for duodenal ulcer should continue for at least 4 weeks; for gastric ulcer 6 weeks; for reflux disease 8-12 weeks.

Prophylaxis of Recurrent Duodenal Ulcer: 400 mg at bedtime or 300 mg twice a day, at breakfast and bedtime. Therapy should continue for at least 6-12 months.

UPPER GASTROINTESTINAL HEMORRHAGE

If bleeding is of sufficient magnitude as to require blood transfusions, 'Tagamet' should be administered parenterally, preferably by intravenous or intermittent infusion, until 48 hours after active bleeding has stopped. Oral administration may then be instituted.

Oral: 600 mg twice a day (at breakfast and bedtime) or 300 mg every 6 hours.

Intramuscular Injection: 300 mg every 6 hours.

Intravenous Injection: 300 mg every 6 hours. Dilute 'Tagamet' in Sodium Chloride Injection 0.9% (or other compatible i.v. solution) to a total volume of 20 mL; inject slowly over at least 2 minutes. Avoid this method in patients with cardiovascular disease.

Intermittent intravenous infusion: 300 mg every 6 hours. Dilute 'Tagamet' in 100 mL of Dextrose Injection 5% (or other compatible i.v. solution); infuse over 15-20 minutes. If necessary, increases should be made by more frequent administration of a 300 mg dose; total daily dose should not exceed 2400 mg.

PATHOLOGICAL HYPERSECRETORY CONDITIONS

(e.g., Zollinger-Ellison Syndrome) 300 mg four times a day, with meals and at bedtime. It may be necessary to administer higher or more frequent doses to control symptoms. If intravenous administration is required, refer to schedule under UPPER GASTROINTESTINAL HEMORRHAGE.

PROPHYLAXIS OF STRESS ULCERATION

300 mg intravenously every 6 hours, or more frequently to maintain a gastric pH above 4. (See Intravenous administration above.)

PROPHYLAXIS OF ACID ASPIRATION PNEUMONITIS

Emergency surgery: 300 mg intramuscularly 1 hour before induction of anesthesia and 300 mg intramuscularly or intravenously every 4 hours until patient responds to verbal commands.

Elective surgery: As above, but an oral dose of 300 mg may be given the night before the operation.

For intravenous administration refer to schedule under UPPER GASTROINTESTINAL HEMORRHAGE.

DOSAGE ADJUSTMENT FOR PATIENTS WITH IMPAIRED RENAL FUNCTION

300 mg every 12 hours orally or intravenously. If required, frequency of dosing may be increased to every 8 hours or further with caution. In severe renal failure the lowest frequency of dosing compatible with an adequate patient response should be used. Liver impairment may necessitate further reductions.

Hemodialysis: More than 80% of a 300 mg intravenous dose is cleared in one 4 hour period of hemodialysis. If possible, adjust dosage schedule to coincide with end of hemodialysis.

Peritoneal dialysis: 'Tagamet' is not removed to any appreciable extent.

STABILITY OF INJECTABLE FORM

'Tagamet' Injection, when added to or diluted with most intravenous solutions, is stable for 48 hours at room temperature.

'Tagamet' Injection should not be refrigerated.

AVAILABILITY

Tablets: 200, 300, 400 and 600 mg cimetidine.

Liquid: Cimetidine hydrochloride equivalent to 300 mg cimetidine per 5 mL. (Alcohol content 2.85% v/v.)

Injection: Cimetidine hydrochloride equivalent to 300 mg cimetidine per 2 mL.

Product Monograph available to physicians and pharmacists on request.

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SMITH KLINE & FRENCH CANADA LTD.
Mississauga, Ontario L5N 2V7

The gentle power of **Rhinalar**[®]

flunisolide solution 0.025% nasal mist:
Corticosteroid

Action: Flunisolide is a corticosteroid with anti-inflammatory topical activity on the nasal mucous membrane with minimal associated systemic activity at the low spray doses administered.

Indications: RHINALAR is indicated for treatment of perennial and seasonal allergic rhinitis when tolerance to or effectiveness of conventional treatment is unsatisfactory.

Contraindications:

1. Active or quiescent tuberculosis or untreated fungal, bacterial or viral infections
2. Hypersensitivity to the product
3. Children under 6 years of age

Warnings:

1. Glucocorticoids may mask some signs of infection, and new infections may appear during their use.
2. The safety of RHINALAR in pregnancy has not been established. Use of RHINALAR during the first three months of pregnancy is not recommended. If used during the second and third trimester, the expected benefits should be weighed against the potential hazards to the fetus.
3. In patients previously on high doses of systemic steroids, withdrawal of steroids may cause symptoms such as tiredness, aches and pains and depression. In severe cases adrenal insufficiency may occur necessitating a temporary resumption of systemic steroids.

Precautions:

1. Replacement of systemic steroids with RHINALAR should be gradual and carefully monitored by the physician.
2. Although absorption sufficient to produce systemic effects has not been shown in clinical studies with RHINALAR Nasal Mist, the potential of adrenal suppression still exists and this must be considered as a possibility with prolonged excessive usage. Patients on long-term therapy should be reassessed periodically to avoid unnecessary continued use.
3. Since onset of action may be somewhat slower than topical or oral sympathomimetic amines or antihistamines, RHINALAR should be used for several days before evaluating therapy.
4. If beneficial effect is not evident after approximately 7 days, the patient should be re-evaluated.
5. If hypersensitivity reactions occur during therapy, the drug should be discontinued and appropriate treatment should be instituted.
6. Corticosteroid therapy can decrease resistance to localized infection. If nasopharyngeal infections occur during therapy, appropriate treatment should be instituted.
7. Despite the very low level of absorption of flunisolide administered intranasally, the following must be kept in mind:
 - a. corticosteroid effects may be enhanced in patients with hypothyroidism and in those with cirrhosis
 - b. in hypoproteinaemia, acetylsalicylic acid should be used cautiously in conjunction with corticosteroids
8. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.
9. During local corticosteroid therapy, the possibility of atrophic rhinitis and/or pharyngeal candidiasis should be kept in mind.

Adverse Reactions: Side effects noted with RHINALAR have been consistent with what one would expect in applying a topical medication to an already inflamed membrane. The most frequent side effect observed was a mild transient nasal burning and stinging. Occasionally this was severe enough to warrant discontinuation of RHINALAR therapy. Other side effects seen in patients treated with RHINALAR in order of decreasing prevalence were: nasal irritation, epistaxis, runny and stuffy nose, sore throat, hoarseness and throat irritation. Exceptionally these may require discontinuation of therapy.

Symptoms and Treatment of Overdosage: Acute overdosage has not been reported. When used at excessive doses, the potential of steroid effects such as hypercorticism and adrenal suppression does exist. Decreasing the dose will abolish these manifestations.

Dosage and Administration: RHINALAR Nasal Mist is for administration by the intranasal route only.

Usual Starting Dose: Adult: 2 sprays (each approximately 25 µg) into each nostril twice a day. Increase to maximum 3 times a day if needed. Children: For children 6 to 14 years of age, one spray (approximately 25 µg) into each nostril 3 times daily.

Maintenance Dose: After the desired clinical effect is obtained, the maintenance dose should be the smallest amount necessary to control the symptoms. Some patients may be maintained on as little as one spray (approximately 25 µg) to each nostril per day. Patients on long-term therapy should be reassessed periodically to avoid unnecessary continued use. There is no evidence that exceeding the maximum recommended dosage is more effective. Therefore, maximum daily dose should not exceed 6 sprays in each nostril for adults and 3 sprays in each nostril for children under 14 years of age.

The effect of RHINALAR, unlike that of vasoconstrictors, is not immediate. Full therapeutic benefit requires regular usage. The absence of an immediate effect should be explained to the patient in order to ensure cooperation and continuation of treatment with the regular dosage schedule.

In the presence of excessive nasal mucus secretion or edema of the nasal mucosa, the drug may fail to reach the site of action. In such cases it is advisable to use a nasal vasoconstrictor for two or three days prior to RHINALAR.

Dosage Form: RHINALAR Nasal Mist is an 0.025% aqueous solution of flunisolide in a 25 ml plastic bottle fitted with a metered pump device which delivers approximately 25 µg of flunisolide per spray via a nozzle which is inserted into the nostril. Flunisolide is dissolved in an aqueous solution containing propylene glycol, polyethylene glycol, citric acid, sodium citrate and benzalkonium chloride as a preservative. It contains no fluorocarbons.

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scribing pattern to a more desirable one, including greater use of short-acting benzodiazepines, at lower doses, for shorter periods of time.¹³

Diazepam and chlorthalidopoxide should not be given by the IM route because of erratic and incomplete absorption.² If an IM injection is required, lorazepam is best. In the elderly, and in patients with liver disease or low serum albumen, the short-acting drugs such as lorazepam or oxazepam are preferable.

Alternate Solutions

Lastly, further study is required to learn why certain populations are such frequent recipients of benzodiazepine prescriptions. Alternative solutions are needed for women, single parents, the elderly, the poor and the uneducated, in dealing with anxiety and stresses partly caused by social factors and vocational and role conflicts. Ideally, specific interventions must be developed to replace the non-specific symptomatic relief that the benzodiazepines offer. ●

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